

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)
20 August 1999 (20.08.99)

International application No.
PCT/US99/00371

Applicant's or agent's file reference
6137.P CP

International filing date (day/month/year)
12 January 1999 (12.01.99)

Priority date (day/month/year)
16 January 1998 (16.01.98)

Applicant

QUINN, Cheryl, L. et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
21 July 1999 (21.07.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Sean Taylor

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/00371

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/63 C12N15/90 C12Q1/68 C12Q1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAMILLI, ANDREW ET AL: "Use of genetic recombination as a reporter of gene expression." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994) VOL. 91, NO. 7, PP. 2634-2638. ISSN: 0027-8424., XP000197110	1-58,60, 62,65-77
X	see the whole document ---	59,61,64
Y	SKERRA, ARNE: "Use of the tetracycline promoter for the tightly regulated production of a murine antibody fragment in Escherichia coli." GENE (AMSTERDAM), (1994) VOL. 151, NO. 1-2, PP. 131-135. ISSN: 0378-1119., XP004042624	1-58, 65-77
X	see the whole document ---	59-63
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 June 1999

Date of mailing of the international search report

21/06/1999

Name and mailing address of the ISA

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Authorized officer

Hix, R

INTERNATIONAL SEARCH REPORT

Inter. .onal Application No

PCT/US 99/00371

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RAMAKRISHNAN, GIRIJA ET AL: "A tetracycline -inducible gene expression system in Entamoeba histolytica." MOLECULAR AND BIOCHEMICAL PARASITOLOGY, (1997) VOL. 84, NO. 1, PP. 93-100 ISSN: 0166-6851., XP002105109	1-58,60, 62,65-77
X	see the whole document	59,61, 63,64
Y	KIM, HONG-JIN ET AL: "Tetracycline repressor- regulated gene repression in recombinant human cytomegalovirus." JOURNAL OF VIROLOGY, (1995) VOL. 69, NO. 4, PP. 2565-2573. ISSN: 0022-538X., XP002037393	1-58,60, 62,63, 65-77
X	see the whole document	59,61,64
Y	M. GOSSEN ET AL.: "Transcriptional activation by tetracyclines in mammalian cells." SCIENCE, vol. 268, 23 June 1995, pages 1766-1769, XP002105110	1-58,60, 62,63, 65-77
X	see the whole document	59,61,64
Y	M. GOSSEN ET AL.: "Tight control of gene expression in mammalian cells by tetracycline-responsive promoters." PROC. NATL. ACAD. SCI. USA, vol. 89, June 1992, pages 5547-5551, XP000564458	1-58,60, 62,63, 65-77
X	see the whole document	59,61,64
Y	US 5 464 758 A (M. GOSSEN ET AL.) 7 November 1995	1-58,60, 62,63, 65-77
X	cited in the application see the whole document	59,61,64
Y	WO 96 40979 A (MICROCIDE PHARMACEUTICALS INC.) 19 December 1996	1-77
	cited in the application see the whole document	
Y	US 5 654 168 A (H. BUJARD ET AL.) 5 August 1997	1-58,60, 62,63, 65-77
X	see the whole document	59,61,64
Y	WO 94 29442 A (BASF AKTIENGESELLSCHAFT) 22 December 1994	1-58,60, 62,63, 65-77
X	see the whole document	59,61,64
3 Y	WO 96 01313 A (DECONTI) 18 January 1996	1-77
	see the whole document	
2	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/00371

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 40946 A (YALE UNIVERSITY) 19 December 1996	1-58,60, 62,63, 65-77 59,61,64
X	see the whole document ---	
A	W. HILLEN AND A. WISSMANN: "Protein-Nucleic Acid Interaction; Tet repressor-tet operator interactions," 1989, SAEGER & HEINEMANN, EDS. MACMILLAN , LONDON XP002105116 cited in the application see page 143 - page 162 ---	
A	M. NESIN ET AL.: "Cloning and nucleotide sequence of a chromosomally encoded tetracycline resistance determinant, tetA(M), from a Pathogenic, Methicillin-resistant strain of Staphylococcus aureus." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 34, no. 11, November 1990, pages 2273-2276, XP002105111 see the whole document ---	
A	T. NGUYEN ET AL.: "Sequence homology between the tetracycline-resistance determinants of Tn10 and pBR322" GENE, vol. 25, 1983, pages 83-92, XP002105112 see the whole document ---	
A	A. EAST ET AL.: "Cloning and sequence determination of six Staphylococcus aureus beta-lactamases and their expression in Escherichia coli and Staphylococcus aureus." JOURNAL OF GENERAL MICROBIOLOGY, vol. 135, 1989, pages 1001-1015, XP002067243 see the whole document ---	
P,Y	P. GHERSA ET AL.: "Highly controlled gene expression using combinations of tissue-specific promoter, recombinant adenovirus and a tetracycline-regulatable transcription factor." GENE THERAPY, vol. 5, no. 9, September 1998, pages 11213-1220, XP002105114	1-58,60, 62,63, 65-77
X	see the whole document ---	59,61,64
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PCT/US 99/00371

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	F. YAO ET AL.: "Tetracycline Repressor, tetR, rather than the tetR-Mammalian cell transcription factor fusion derivatives, regulates inducible gene expression in mammalian cells." HUMAN GENE THERAPY, vol. 9, no. 13, 1 September 1998, pages 1939-1950, XP002105115	1-58, 60, 62, 63, 65-77
X	see the whole document -----	59, 61, 64

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 00371

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 77
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful international Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

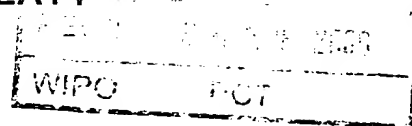
International Application No

PCT/US 99/00371

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5464758 A	07-11-1995	US 5789156 A	04-08-1998
		US 5589362 A	31-12-1996
		US 5814618 A	29-09-1998
		US 5866755 A	02-02-1999
WO 9640979 A	19-12-1996	AU 5939996 A	30-12-1996
		CA 2223519 A	19-12-1996
		EP 0830457 A	25-03-1998
US 5654168 A	05-08-1997	AU 3092395 A	25-01-1996
		CA 2193122 A	18-01-1996
		CN 1167504 A	10-12-1997
		EP 0804565 A	05-11-1997
		FI 965287 A	28-02-1997
		NO 965623 A	28-02-1997
		WO 9601313 A	18-01-1996
		US 5789156 A	04-08-1998
		US 5589362 A	31-12-1996
		US 5814618 A	29-09-1998
		US 5866755 A	02-02-1999
WO 9429442 A	22-12-1994	AU 684524 B	18-12-1997
		AU 7108194 A	03-01-1995
		CA 2165162 A	22-12-1994
		EP 0705334 A	10-04-1996
		JP 9500526 T	21-01-1997
		US 5650298 A	22-07-1997
		US 5789156 A	04-08-1998
		US 5888981 A	30-03-1999
		US 5859310 A	12-01-1999
		US 5589362 A	31-12-1996
		US 5814618 A	29-09-1998
		US 5866755 A	02-02-1999
WO 9601313 A	18-01-1996	US 5654168 A	05-08-1997
		US 5789156 A	04-08-1998
		US 5866755 A	02-02-1999
		AU 3092395 A	25-01-1996
		CA 2193122 A	18-01-1996
		CN 1167504 A	10-12-1997
		EP 0804565 A	05-11-1997
		FI 965287 A	28-02-1997
		NO 965623 A	28-02-1998
		US 5589362 A	31-12-1996
		US 5814618 A	29-09-1999
WO 9640946 A	19-12-1996	US 5851796 A	22-12-1998
		AU 6274596 A	30-12-1996
		EP 0832254 A	01-04-1998

PATENT COOPERATION TREATY

PCT



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)


Applicant's or agent's file reference 6137.P CP		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FOR FURTHER ACTION		
International application No. PCT/US99/00371	International filing date (day/month/year) 12/01/1999	Priority date (day/month/year) 16/01/1998
International Patent Classification (IPC) or national classification and IPC C12N15/63		
Applicant PHARMACIA & UPJOHN COMPANY et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 6 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 21/07/1999	Date of completion of this report 29.03.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer van Heusden, M Telephone No. +49 89 2399 8145 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/00371

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Description, pages:

1-30 as originally filed

Claims, No.:

1-77 as originally filed

Drawings, sheets:

1/14-14/14 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/00371

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-58, 60-77
	No:	Claims	59
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-77
Industrial applicability (IA)	Yes:	Claims	21-76
	No:	Claims	1-20, 77 (?)

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/00371

Additional remarks to section V:

1. Citations

The documents mentioned in this IPER are numbered as in the International Search Report (ISR), i.e. D1 corresponds to the first document of the ISR etc.

2. Novelty (Article 33(2) PCT)

- 2.1 The present application discloses a process to allow the characterization of an essential microbial gene using a tetracycline-controllable element (TCE).
- 2.2 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject matter of claim 59 is not novel in respect of documents D4-D7. These documents disclose a tetracycline-controllable transcription promoter polynucleotide sequence (a promoter including a tet-operator) operably linked to a microbial gene (β -glucuronidase in D4 and β -galactosidase in D5-D7).

3. Inventive step (Article 33(3) PCT)

- 3.1 The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject matter of claims 1-77 does not involve an inventive step in view of documents D8 and D1-D7. The closest prior art to evaluate the inventiveness of claims 1-77 is document D8, which discloses a process to identify an essential microbial gene important to the microbe's ability to infect or sustain an infection in a mammal, by artificially (through genetic alteration) regulating the expression of said gene. The process disclosed in D8 differs from the present application in that the regulatory components used in the specific embodiment are the lac repressor and lac operon. Thus the problem to be solved by the present invention appears to be the provision of a further regulatory system to control the expression of an endogenous microbial gene. D8 suggests the use of other regulatory systems, and specifically suggests the use of tetracycline controllable elements (p. 40, l. 10-12; p. 41, l. 11-12; p. 54, l. 15-17). In addition, the tet repressor/tet operon system is well known in the prior art (see D1-D7 and D9-D15) and thus no inventive step is needed to arrive at the subject matter of claims

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/00371

1-77 of the present application.

4. Industrial applicability (Article 33(4) PCT)

The subject matter of claims 21-76 is industrially applicable.

The subject matter of claims 1-20 and 77 includes methods of treatment of the human or animal body and is thus excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT. For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exist in PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The applicant is already informed that in the case of a European application, claims 1-20 and 77 are not allowable because 'methods of treatment of human or animal body by surgery or by therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application'.

Additional remarks to section VIII:

The following objections are raised under **Article 6 PCT** concerning the clarity of the claims:

1. The dependence of many of the claims is incorrect: e.g. claim 16 refers to the recombinant bacterium of claim 1, in which there is no reference to a recombinant bacterium. Claim 17 relates to the Staphylococcus species of claim 1, in which there is no reference to a Staphylococcus species. Claims 37 and 38 refer to the reporter gene of claim 21, in which there is no reference to a reporter gene. Claims 39 and 40 refer to the tetracycline resistance protein of claim 21, in which there is no reference to a tetracycline resistance protein. Claim 41 relates to the

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/00371

tetracycline repressor of claim 21, in which there is no reference to a tetracycline repressor.

2. Several claims are redundant or contain redundant wording: e.g. claim 36 is identical to claim 34. The subject matter of claim 25 is an embodiment of claim 43. Similarly, claim 27 is an embodiment of claim 44. Claim 45 is identical to claim 29. Also claim 70 is identical to claim 29. Claim 71 is identical to claim 30. Claim 72 is identical to claim 47. Claim 46 is a specific embodiment of the DNA molecule of claim 21 and should therefore depend on claim 21. The same applies to claim 59. In summary, the dependency of the claims absolutely lacks clarity and the wording of the claims lacks conciseness in that undue repetition of wording is used throughout the claims.
3. Apart from TCE, also the tet-repressor and the tet-resistance genes are essential features of the present alleged invention, which features are lacking from the independent claims.
4. The subject matter of claims 76 and 77, in which a reference to TCE is lacking, lacks clarity in that it is not clear how they relate to the remainder of the application. In fact, 'growing E. coli in the presence of tetracycline' falls within the scope of claim 76 (the E. coli tet resistance gene being an endogenous prokaryotic gene regulated by tetracycline).